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Imaging Techniques for Treatment Evaluation for Metastatic Breast Cancer

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Investigators:

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies and strategies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

This EPC evidence report is a Technical Brief. A Technical Brief is a rapid report, typically on an emerging medical technology, strategy or intervention. It provides an overview of key issues related to the intervention—for example, current indications, relevant patient populations and subgroups of interest, outcomes measured, and contextual factors that may affect decisions regarding the intervention. Although Technical Briefs generally focus on interventions for which there are limited published data and too few completed protocol-driven studies to support definitive conclusions, the decision to request a Technical Brief is not solely based on the availability of clinical studies. The goals of the Technical Brief are to provide an early objective description of the state of the science, a potential framework for assessing the applications and implications of the intervention, a summary of ongoing research, and information on future research needs. In particular, through the Technical Brief, AHRQ hopes to gain insight on the appropriate conceptual framework and critical issues that will inform future comparative effectiveness research.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome comments on this Technical Brief. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

Richard G. Kronick, Ph.D.
Director
Agency for Healthcare Research and Quality

Jean Slutsky, P.A., M.S.P.H.
Director, Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Stephanie Chang, M.D., M.P.H.
Director
Evidence-based Practice Program
Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Elise Berliner, Ph.D.
Task Order Officer
Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

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Key Informants

In designing the study questions, the EPC consulted a panel of Key Informants who represent subject experts and end-users of research. Key Informant input can inform key issues related to the topic of the technical brief. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches and/or conclusions do not necessarily represent the views of individual Key Informants or their organizations.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any conflicts of interest.

The list of Key Informants who participated in developing this report follows:
<Name>
<Place>
<City>, <ST>

Peer Reviewers

Prior to publication of the final evidence report, EPCs sought input from independent Peer reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report does not necessarily represent the views of individual reviewers.

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The list of Peer Reviewers follows:
<Name>
<Place>
<City>, <ST>

<Name>
<Place>
<City>, <ST>

Imaging Techniques for Treatment Evaluation for Metastatic Breast Cancer

Structured Abstract

Background. Although multiple imaging modalities to evaluate treatment response in patients with metastatic breast cancer are used clinically, their comparative effectiveness has not been determined.

Purpose. The purpose of this technical brief is to understand current utilization of metastatic breast imaging modalities used for treatment evaluation in the United States in order to summarize the current state of the science and inform future research on this topic.

Methods. We worked with Key Informants, including clinicians, patient advocates, representatives from the device manufacturing industry, and a product purchaser. Additionally, we searched gray and published literature from 2003–2013. We qualitatively synthesized the information from the Key Informant interviews and the gray literature. From the published literature, we abstracted data on the types of imaging used to evaluate treatment of metastatic breast cancer.

Findings. We identified bone scan (scintigraphy), magnetic resonance imaging (MRI), computed tomography (CT), and fluorodeoxyglucose-positron emission tomography (FDG-PET)/CT as the major modalities used for treatment evaluation of metastatic breast cancer in the United States. We also identified four types of imaging not commonly used currently that might become important within the next decade: F-fluoromisonidazole-(F-FMISO) PET/CT, fluorothymidine-(FLT) PET/CT, fluoroestradiol-(FES) PET/CT, and PET/MRI. All published reports pertaining to imaging evaluation of treatment response among metastatic breast cancer patients were limited to small, nonrandomized studies. Future research on novel radiotracers and biomarkers may clarify breast tumor biology. Additionally, future studies should address the lack of information on patient-centered outcomes and costs of imaging for treatment response for metastatic breast cancer.

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Background

Introduction

In spite of significant gains in detection and treatment, breast cancer continues to have a broad impact in the United States, with an estimated 234,580 individuals with new diagnoses in 2013.[1] About 33 percent of individuals with breast cancer diagnosed between 2001 and 2007 had regional metastases, with a 5-year relative survival rate of 84 percent. Approximately 5 percent were diagnosed with distant metastases, most commonly to the bones, lungs, liver, or brain, and had a 5-year relative survival rate of only 23 percent.[1]

Several imaging modalities, including magnetic resonance imaging (MRI), computed tomography (CT), positron emission tomography (PET), PET/CT, and bone scintigraphy, are used to evaluate the effects of treatment for metastatic breast cancer.[2] However, as outlined in guidelines from the National Comprehensive Cancer Network and the National Institute for Health and Clinical Excellence, evidence regarding the accuracy and effectiveness of these modalities to evaluate treatment of metastatic breast cancer is lacking, even though the type and results of imaging may strongly affect patient outcomes.[2,3] Inappropriate use could lead to overtreatment. For example, use of CT during treatment response monitoring may show morphologic or size changes in the tumor in the setting of nonresponse, leading to continued ineffective and potentially toxic chemotherapy. Alternatively, inappropriate use of imaging may lead to undertreatment if foci of enlarging metastatic disease are not identified on CT and these lead to disease progression. Furthermore, imaging modalities vary substantially in cost, ranging in direct costs from about $250 for a bone scan to $1,114 for PET/CT,[4,5] underscoring the need to understand whether more expensive tests result in improved patient outcomes.

Current Practices in Imaging Metastatic Breast Cancer

Health care providers generally rely on recommendations from professional societies such as the National Comprehensive Cancer Network, the American Society for Clinical Oncology, and the European Society for Medical Oncology to guide the use of imaging techniques to assess treatment response in metastatic breast cancer. However, these recommendations are generally based on data that is not specific to assessing treatment in the metastatic breast cancer population. Current practice recommendations for managing metastatic breast cancer include imaging of the chest, abdomen, and bone in addition to obtaining medical histories, physical examinations, and relevant laboratory tests.[6,7] The most commonly used imaging modalities for treatment evaluation of metastatic breast cancer are chest/abdomen/pelvis CT and PET/CT.[6,7] For patients with bone-only metastases, bone scans are the most common imaging modality, with supplemental use of CT, MRI, and/or PET/CT to evaluate localized symptoms.[7,8]

Objective of Technical Brief

Although multiple imaging modalities for treatment evaluation for metastatic breast cancer are used clinically, their comparative effectiveness in terms of health outcomes, patient satisfaction, or cost, has not been determined. The purpose of this technical brief is to understand current utilization, emerging technologies, research in progress, patient values, and study design issues, in order to summarize the current state of the science and inform future research in this area. We also evaluated whether certain imaging technologies may be more suitable for some subpopulations and attempt to determine if the technologies are being used appropriately. Although we asked Key Informants about the role of biomarkers in imaging for treatment evaluation of metastatic breast cancer, a thorough exploration of emerging biomarkers and other nonimaging tests is beyond the scope of this technical brief. We combined information we obtained from published literature, gray literature, and Key Informants in order to provide the context for appropriate comparative effectiveness studies on imaging for treatment evaluation for metastatic breast cancer in the near future.

Guiding Questions

The questions below guided the data collection for this technical brief. Question 1 laid the groundwork for the literature review by describing each of the imaging modalities currently in use for treatment evaluation for metastatic breast cancer. We describe the accuracy, potential benefits, and potential risks of each modality, including safety, costs, adverse effects, and other issues. Question 2 provided the context for how each of the imaging modalities is currently used, including U.S. Food and Drug Administration (FDA) approval status, need for additional equipment (e.g., contrast agents), and, when possible, we describe reimbursement policies and how commonly each modality is used for metastatic breast cancer treatment evaluation. Using published studies and gray literature, Question 3 explores the state of the current research on the use and safety of each imaging modality. Finally, in Question 4, we identify important issues pertaining to metastatic breast cancer imaging, particularly areas of uncertainty surrounding ethical, economic, and safety issues, as well as areas of research that we expect to be pursued in the near future.

Guiding Question 1. Overview of Imaging Modalities Currently Used to Evaluate Treatment of Metastatic Breast Cancer

- What are the imaging modalities currently used for metastatic breast cancer treatment evaluation in the United States?
- What are the advantages and disadvantages (e.g., safety issues, cost) of each modality?

Guiding Question 2. Context in which Imaging Modalities are Currently Used to Evaluate Treatment of Metastatic Breast Cancer

- What is the FDA status of each modality?
- What other resources (e.g., contrast agents) are commonly used with each modality?
- How commonly is each modality used?

Guiding Question 3. Current Evidence for Each Imaging Modality

- What published and unpublished studies have reported on the use and safety of each modality? When describing each study, include:
    a. Patient population (inclusion/exclusion criteria, age, race, cancer characteristics)
    b. Study design/size
    c. Concurrent and prior imaging modalities used
    d. Length of followup
    e. Outcomes measured (survival, recurrence, others)
    f. Adverse events or harms reported.

Guiding Question 4. Important Issues and Future Directions of Metastatic Breast Cancer Imaging for Treatment Evaluation

- Given the current state of the science, what are the implications for future diffusion of the imaging modalities for treatment evaluation of metastatic breast cancer?
- What are the economic, ethical, and privacy considerations that impact the diffusion of each imaging modality?
- What are important areas of uncertainty for metastatic breast cancer imaging modalities?
- What research questions would have the greatest impact for women with metastatic breast cancer?

Methods

Overview

This technical brief combined systemic literature review approaches with Internet searches and Key Informant discussions.

Search Strategy

We first used broad search terms including Medical Subject Heading terms and key words related to imaging, metastatic breast cancer, and treatment evaluation. We conducted focused searches of PubMed® and the Cochrane Library. An experienced research librarian assisted us in choosing the search terms and limits (Appendix A). We also reviewed the reference lists of identified publications and added previously unidentified papers.

From these identified articles, we excluded publications that were beyond the scope of the technical brief (letters, comments, editorials, news, nonhuman studies, and articles not in English). Because imaging technologies are rapidly evolving, we excluded studies published prior to 2003. Searches were also conducted in a number of imaging and oncologic websites, including the American Society for Clinical Oncology, the American College of Radiology, the American Cancer Society, the National Comprehensive Cancer Network, and the Society for Nuclear Medicine. We also searched ClinicalTrials.gov, NIH Reporter, and ProQuest Dissertations and Theses to find unpublished studies. As in the published literature search, we excluded gray literature sources that were published prior to 2003, those that pertained to animal studies and those that were not in English.

Eligibility Criteria

The inclusion and exclusion criteria are presented in Table 1. All titles and abstracts identified through searches were reviewed against our inclusion/exclusion criteria. For studies without adequate information to make a determination, we retrieved full-text articles and reviewed them against the inclusion/exclusion criteria.

Table 1. Inclusion and exclusion criteria for imaging of metastatic breast cancer published literature search

Criterion	Inclusion	Exclusion
Population	Age 19 and above Females Diagnosed with metastatic (stage IV) breast cancer (initial diagnosis or recurrence)	Age 18 and below Males Diagnosed with stages I-III breast cancer Nonhuman
Indication for imaging	Imaging for treatment evaluation	Diagnostic imaging Imaging used to assess stage Imaging used to detect recurrence following successful treatment
Comparator	Comparison of multiple imaging modalities Tumor biomarkers No comparator	None
Outcomes associated with imaging findings	Tumor response Changes in treatment decisions Changes in patient decisions Recurrence-free survival Overall survival Quality of life Cost and resource utilization Adverse events	None
Timing	Published 2003-2013	Published 2002 or earlier
Setting	All care settings	None
Study design	Systematic reviews Randomized control trials Non-randomized control trials Cohort studies (prospective and retrospective) Case-control studies Case series	Case reports Opinions Commentaries Letters to the editor with no primary data
Other	English language	Non-English language

Two team members (LG and CL) abstracted data from the published studies to provide an overview of the state of the science by collecting the following information:

- Study setting and geographic location
- Research design and methods
- Type(s) of imaging
- Breast cancer inclusion criteria
- Tumor factors (e.g., whether metastatic tumors were initially diagnosed or were recurrences)
- Comparators used
- Length of followup
- Outcomes associated with imaging findings (accurate detection of tumor response, changes in treatment decisions, prediction for survival, resource utilization, and adverse events).

Key Informant Discussions

We worked with the Key Informants to understand current utilization, emerging technologies, research in progress, patient values, and study design issues, in order to help summarize the current state of the science and inform future research on imaging for treatment evaluation for women with metastatic breast cancer. We identified Key Informants including clinical experts/practitioners in radiology and oncology, representatives of patient perspectives, a product purchaser, and representatives from device industries. Key Informants were identified through informal consultations with local, national, and international experts in breast cancer and imaging technologies in general. While we attempted to schedule more than one Key Informant per teleconference, most (n=5) calls consisted of only one Key Informant. Calls were led by one team member and at least two other team members participated. All calls were recorded for reference.

Initially, we asked the Key Informants to create a comprehensive list of imaging technologies, including technologies not commonly used but that are in development and may be used in the United States in the near future. We also asked them to identify the advantages and disadvantages and appropriateness of utilization of each type of imaging. Key Informants were asked to identify factors surrounding imaging decisions, including clinical guidelines, reimbursement policies, setting (e.g., tertiary care vs. community hospital), and patient preferences. The Key Informants also provided information about factors that patients consider when discussing imaging decisions with their providers such as test accuracy and invasiveness, safety issues, and out-of-pocket costs.

Findings

Overview

The availability of quantitative or qualitative data to address the guiding questions from our Key Informant interviews and the published and gray literature searches is presented in Table 2. Four imaging modalities are currently used in the United States for evaluating treatment response for metastatic breast cancer: bone scan, MRI, CT, and fluorodeoxyglucose (FDG)-PET/CT. We also identified four types of imaging not commonly used currently that might become important in the next 5–10 years: fluorothymidine (FLT)-PET/CT, F-fluoromisonidazole (F-FMISO)-PET/CT, fluoroestradiol (FES)-PET/CT, and PET/MRI.

In total, we interviewed nine Key Informants: five were clinicians, two were from product industry development companies, one was a patient advocate, and one provided both product purchaser and patient advocate perspectives. Three clinicians and one patient advocate were interviewed in the same phone call; all remaining calls were with only one Key Informant. Interviews lasted between 40–60 minutes and consisted of 8–13 questions. All interviews took place in October and November 2013. A summary of the interviews appears in Appendix B.

A summary of the findings from the published literature search is shown in Table 3 and the abstracted data are shown in Table 4. A full list of included and excluded studies is shown in Appendixes C and D. We abstracted data from a total of 16 publications.[9-24] Where the two abstractors disagreed, a discussion was performed to come to conclusions. The study populations from seven publications were from the United States,[9,14,19,20,22-24] eight were from Europe,[10,12,13,15-18,21] and one was from Asia.[11] All were cohort studies, of which seven were retrospective[10,14,17,19,20,23,24] and nine were prospective.[11-13,15,16,18,21,22] Eleven of 18 studies[10-18,20,22] presented comparators pertaining to the type of imaging used; seven of these[10,13,15,16,18,20,22] compared tumor response as measured by tracer uptake to response measured by anatomic imaging. Four studies[12,14,17,22] compared tumor response measured by tracer uptake to measures of tumor biomarkers. One study[11] compared tumor response as measured by two types of tracers (FDG- vs. F-FMISO-PET/CT). Almost all of the studies (15 of 16)[9-13,15-24] reported accuracy in detecting tumor response as an outcome. Six[9,10,14-16,21] reported overall survival and three[14,17,23] reported progression-free survival. No studies reported recurrence-free survival, changes in treatment decisions, changes in patient decisions, quality of life, cost and resource utilization, or adverse events related to imaging. Only one study[20] distinguished metastatic breast cancers that were initially diagnosed from those that were recurrences from non-metastatic breast cancers. In total, the published literature reported on the imaging experiences of 528 women with metastatic breast cancer in the United States, Asia, and Europe. We estimate that approximately 792,000 women in the United States received imaging scans for the purpose of evaluating treatment of metastatic breast cancer (see Appendix E for details on this calculation) between 2003-2013, and thus the number of women enrolled in clinical studies to evaluate the benefits and harms of imaging for this purpose represented less than 0.1 percent of the women exposed to these procedures.

Finally, a summary of the findings from the gray literature search are shown in Table 5. We identified three current or soon-to-be recruiting clinical trials pertaining to imaging for treatment evaluation for metastatic breast cancer.

Summary of Imaging Trends for Treatment Evaluation of Metastatic Breast Cancer

The Key Informants generally agreed that the trend of imaging for evaluation of treatment of metastatic breast cancer was toward stable or increased utilization; none speculated that imaging for this purpose would decrease in the near future. Additionally, most payers readily reimburse for CT, PET-CT, bone scans, and other imaging modalities that are appropriate to the regions of the body where the metastases are located. However, some payers advocate for programs such as the use of Radiology Benefit Managers or peer-to-peer consultations, which often result in discouraging physicians from ordering imaging. Whether these programs lead to more appropriate utilization is unclear. Several Key Informants also indicated that use of PET-CT is likely influenced by the purchase of the expensive machinery and once the investment in the technology has been made, the scans will be used for many other indications besides treatment evaluation of metastatic breast cancer.

The Key Informants also reported that, compared with academic settings, imaging in community practices is probably more variable and patient preparation and physician interpretation are often inferior in a community setting. One indicated that insurance status might be more of a factor in community settings, with non- or underinsured patients being steered toward less expensive imaging. However, another Key Informant thought that physicians in academic centers might feel greater pressure to use more complicated and expensive technologies for fear of reprisals if they failed to order tests.

Summary of Shared Decisionmaking Regarding Imaging for Treatment Evaluation of Metastatic Breast Cancer

We did not find any published literature regarding patient involvement in decisionmaking regarding imaging for treatment evaluation of metastatic breast cancer. However, our Key Informants provided some information on this topic. They indicated that imaging is usually not the focus of patient education, both in terms of conversations that patients have with their care providers and the research that patients conduct on their own. Additionally, since physicians who interpret images usually interact with the ordering physicians rather than the patients themselves, patients are often under-informed about imaging and usually are not aware that they can engage in shared decisionmaking with their physicians regarding treatment evaluation by imaging.

Our Key Informants indicated that many patients are accustomed to receiving PET/CT and would not agree with receiving imaging followup only by CT after receipt of a previous PET/CT. Our Key Informants also reported that physicians might prefer to order tests based on their own experiences and biases, rather than spend time debating the merits of alternative imaging strategies with their patients.

Interestingly, the clinicians reported that they sometimes advocated for imaging less often to reduce the stress that patients feel while waiting for imaging results. Both Key Informants who provided the perspective of patient advocates reported that patients receive intangible value from receiving results of imaging scans that show their cancer is improving and are willing to experience the stress and anxiety of waiting for imaging results in order to potentially receive good news about their prognoses. Both patient advocates also reported that breast cancer patients are generally not concerned about the potential harm that could result from imaging, such as exposure to radiation from CT, PET and PET/CT scans, because their therapies already involve such exposures.

Modalities Currently in Use

Bone Scan (Scintigraphy)

Bone scans are used to identify areas of physical and chemical changes in bone throughout the body. A small amount of a radionuclide tracer is injected intravenously and areas of increased tracer uptake may indicate the presence of bone metastases. Although we could not find published data on how commonly bone scans are used to evaluate treatment of metastatic breast cancer, our Key Informants reported that bone scans are almost always used to evaluate treatment in patients who have been diagnosed with bony metastases. The Key Informants also reported that, because bone scans are less expensive than PET/CT, they may be ordered when PET/CT is not covered by the patient's insurance. Some patients prefer bone scans to PET/CT because, in addition to being less expensive, they take less time (about 1 hour vs. about 2 hours, respectively). Bone scans received FDA approval through the Medical Device Amendments of 1976, which allowed devices being clinically used to receive FDA approval without undergoing premarket approval or 510(k) clearance. The most commonly used contrast agent for bone scans is technetium-99m.[25] Safety issues pertaining to bone scans include exposure to radiation from the injected contrast agent and, rarely, the potential for allergic reactions to contrast agents. The Key Informants indicated that most patients were not concerned with exposure to radiation from imaging because their treatments usually entailed much larger doses.

We found only two published studies that described use of bone scans to evaluate treatment of metastatic breast cancer.[10,20] Both compared PET tracer uptake (one evaluated FDG and the other evaluated FES) to bone scans and other types of anatomic imaging to determine tumor response. Although these studies were small (both had n=47), both studies found that the uptake of PET tracers were better predictors of response than bone scans (median response times were 6 and 87 months).[10,20]

Although we did not find specific information about the future directions of bone scans, our Key Informants indicated that the technology was extremely useful and was not likely to be displaced by other technologies in instances of bone metastases. None of the Key Informants prioritized bone scans as a potential topic for future research studies.

Magnetic Resonance Imaging

MRI uses magnetism to produce detailed images. For breast MRI, breast coils are used to improve detection of the emitted signal and to identify potential abnormalities. Gadolinium-based contrast agents are also used to assist with evaluation of breast tumors. MRI scanners, breast coils, and gadolinium-based contrast agents have all received FDA approval.[26]

One advantage of MRI in comparison with other types of imaging such as CT and PET/CT is that it does not involve exposure to radiation.[27] Another advantage that our Key Informants reported was that MRI was useful to evaluate treatment for patients with brain metastases who had received a baseline MRI. A disadvantage of MRI use is that the test may be difficult for claustrophobic patients to tolerate. Additionally, like bone scans, patients can experience allergic reactions to the contrast agents used for MRIs, but these are rare and most reactions are mild.[28] We did not find any quantitative evidence describing how commonly MRI is used to evaluate treatment of metastatic breast cancer.

We identified four published studies[9,15,16,20] that described use of MRI to evaluate treatment of metastatic breast cancer. Three of these compared treatment evaluation using tracer (FDG[15,16] and FES[20]) uptake from PET/CT with imaging using MRI and CT and one did not compare MRI to another method of treatment evaluation.[9] All three studies that compared conventional imaging and tracer uptake found correlations between tumor response using MRI and/or CT and PET radiotracer uptake.[15,16,20] However, only one of these reported data on the correlation between tumor response determined by MRI or CT and overall survival and found no correlation (mean followup time 27 weeks).[16]

Computed Tomography

CT uses digital geometry processing to generate three-dimensional images of structures in the body by taking many two-dimensional images from a single axis of rotation. The data from CT scanners are transmitted to computers, which create three-dimensional cross-sectional pictures. While CT scans are valuable in identifying and anatomically localizing tumors, they have disadvantages such as exposure to ionizing radiation and the potential for adverse effects from iodinated contrast agents, which range from mild (nausea, itching) to severe (cardiopulmonary arrest).[29] Because CT systems were widely used prior to 1976, they received FDA approval through the Medical Device Amendments.[26]

Although we did not find published data on how commonly CT is used to monitor treatment of metastatic breast cancer, the clinical Key Informants reported that this type of imaging was often used, especially in cases when staging PET/CT is not covered by insurance.

We identified six published studies describing use of CT to evaluate treatment of metastatic breast cancer.[10,13,15,16,18,20] Most of these (n=5)[10,13,15,16,18] were conducted in Europe and all compared tracer uptake (FLT,[13,18] FDG,[10,15,16] and FES[20]) from PET/CT to anatomic imaging (including CT). Five of these studies found that uptake of the tracers was associated with changes in tumor volume measured by CT.[13,15,16,18,20] As described in the MRI section, another study reported no significant correlation between conventional imaging using CT or MRI and survival (mean followup time 27 weeks).[16]

Positron Emission Tomography/Computed Tomography

A PET scan uses nuclear medicine imaging to produce three-dimensional color images of functional processes in the body. Several types of tracers have been developed for use with PET, including FDG, F-FMISO, FLT, and FES. FDG is the only tracer approved by the FDA for oncological purposes, and is therefore the most widely used. Because tumors have increased glucose metabolism compared with noncancerous tissue, FDG has the ability to detect tumors on PET imaging. Since 2006, all PET scanners purchased in the United States were combined PET/CT machines.[30] Like bone scans and computed tomography, PET scanners received FDA approval through the 1976 Medical Devices Amendment and combination PET/CT devices received 510(k) clearance in 2000.[26]

Our Key Informants indicated that FDG-PET/CT is currently the most commonly used type of imaging for treatment evaluation of metastatic breast cancer. According to our Key Informants, the main advantage of PET/CT is its ability to combine the functional information from FDG uptake with the higher resolution of CT for determining anatomic location and tumor morphology. Both the PET and CT scans are obtained during the same exam and images are post-processed into a fused series of images. However, the modality does have disadvantages, including the expense of the test and exposure of the patients to ionizing radiation and potentially harmful contrast agents.[31] Largely because of these limitations, our Key Informants reported that they order PET/CT scans no more often than every 2-4 months during treatment for metastatic breast cancer, and only when patients are not obviously responding or worsening clinically.

Although we did not find any quantitative data, our Key Informants noted that PET/CT scans may be inappropriately utilized because the technology is relatively novel. Additionally, the Key Informants felt PET/CT might be underused in community care settings, where access to a PET/CT machine might entail long travel times for patients or ordering physicians might not be accustomed to utilizing the technology.

Although the American College of Radiology provides accreditation of centers that use PET devices, they do not require standard procedures for preparing patients prior to their scan or require minimum volumes that centers must maintain in order to remain accredited (as they do for breast MRI). Furthermore, interpretation of PET/CT scans is not monitored – and guidelines are not enforced – by any accrediting organization, resulting in variable readings. The Key Informants also reported that PET/CTs for breast cancer are used relatively less frequently compared with PET/CTs for other solid organ malignancies, such that even at major cancer centers in large cities, only about 10 percent of the PET/CTs are related to breast cancer. Thus, the experience of PET/CT interpreting physicians for treatment evaluation of metastatic breast cancer may be somewhat limited due to relatively low volumes.

We identified a total of 15 studies describing use of PET to evaluate treatment for breast cancer.[10-24] Ten of these described use of FDG,[10,11,14-17,20,21,23,24] four describe FLT,[12,13,18,22] one described F-FMISO,[11] and two described FES[19,20] (two studies evaluated more than one kind of tracer). Four studies evaluating FDG-PET,[10,15,16,20] two studies evaluating FLT-PET,[13,18] and one study evaluating FES-PET[20] compared tracer uptake values to anatomic imaging with MRI, bone scans, and/or CT, and these are described above.

Four studies compared tracer uptake (two looked at FDG[14,17] and two examined FLT[12,22]) with tumor biomarkers as ways to evaluate response to therapy. One study of 102 metastatic breast cancer patients found circulating tumor cells (CTCs) were correlated with FDG uptake in 67 percent of patients and, in univariate analyses, both FDG uptake and CTCs were predictive of survival; however, in multivariate analysis, FDG uptake was no longer predictive of survival.[14] The other study, conducted in Belgium (n=25), found only 28 percent concordance between FDG uptake and the tumor markers CA15-3 or carcinoembryonic antigen. This study did find a longer progression-free survival in patients who showed response on FDG-PET (11 months) compared with patients who were nonresponders (7 months).[17] For the studies examining FLT, although sample sizes were small (n=14 and n=9), both found correlations between uptake of FLT and tumor markers (CA27.29 and CTCs).[12,22]

Three studies reported on disease progression by level of uptake of FDG.[21,23,24] All reported that standardized uptake values on initial FDG-PET scans were associated with outcomes, including time to disease progression or skeletal-related event (n=28; median followup 17.5 months),[23] response duration (n= 102; median followup=15 months),[24] and progression-free survival (n=22; followup was at least 4 years).[21]

One small study[19] (n=30, 27 of which were women) reported use of FES-PET to compare response to estrogen blocking therapy with estrogen depleting therapy in patients with bone metastases undergoing salvage endocrine therapy. These authors found the standardized uptake value of FES declined 54 percent in patients taking estrogen-blocking therapy and declined only 14 percent for patients taking estrogen-depleting agents.[19]

Finally, one small study[11] (n=12) conducted in China compared use of F-FMISO to FDG-PET. While FDG uptake did not correlate with clinical outcomes, F-FMISO-PET showed a fairly strong correlation (r=0.77).[11]

The Key Informants agreed that PET/CT is one of the most useful oncological imaging tools available. Many Key Informants felt that future research on novel tracers would be fruitful. In particular, the Key Informants indicated that research that revealed more about the underlying biology of breast and metastatic tumors would be useful since breast cancer is a heterogeneous disease. Because patients who do not respond to first line therapy tend not to respond to second, third, or fourth line treatments either, the value of using imaging to discover whether treatment is working early in first line treatment often does not affect long-term outcomes that are important to patients, like survival. Future research on tracers such as FES might shed more light on tumor biology and allow discovery of novel treatments that might be more successful for women with metastatic breast cancer.

Positron Emission Tomography/Magnetic Resonance Imaging

Several of our Key Informants mentioned that combination PET/MRI scanners might become important within the next decade and at least one such device has received FDA approval.[32] However, we did not find any published or gray literature describing use of this modality to evaluate treatment of metastatic breast cancer. Although a major disadvantage of this technology is that it combines two expensive modalities, it might be ideal for imaging of brain metastases. By combining PET's metabolic imaging capabilities with MRI's excellent tissue contrast, the combination may increase accuracy in evaluating response to therapy for brain metastases. Another advantage is that, unlike PET/CT, it would not involve exposure to relatively large amounts of ionizing radiation from the CT component (although it would still entail some radiation exposure from the tracer).[33]

Table 2. Availability of data in Key Informant interviews, published literature, and gray literature to address guiding questions

	Modalities Currently in Use	Modalities Currently in Use	Modalities Currently in Use	Modalities Currently in Use	Investigational	Investigational	Investigational	Investigational
	Bone Scan	**MRI**	**CT**	**FDG-PET/CT**	**FLT-PET/CT**	**F-FMISO-PET/CT**	**FES-PET/CT**	**PET/MRI**
GQ 1: Overview of Imaging Modalities								
a. What modalities are currently being used in the United States?	KI, PL, GL	KI, PL, GL	KI, PL, GL	KI, PL, GL	KI, PL, GL	PL	KI, PL, GL	KI
b. Advantages and disadvantages of each?	KI, PL	KI, PL	KI, PL	KI, PL				
GQ 2: Context of Use								
a. FDA status	PL	PL	PL	PL	PL	PL	PL	PL
b. Contrast agents used	PL	PL	PL	PL	PL	PL	PL	
c. How commonly is modality used?	KI, PL	KI, PL	KI, PL	KI, PL	KI, PL	PL	KI, PL	KI, PL
GQ 3: Current Evidence								
a. Patient population	KI, PL	KI, PL	KI, PL	KI, PL	KI, PL	PL	KI, PL	
b. Study design/size	PL	PL	PL	PL	PL	PL	PL	
c. Concurrent/prior imaging				PL				
d. Length of followup	PL	PL	PL	PL	PL	PL	PL	
e. Outcomes	PL	PL	PL	PL	PL	PL	PL	
f. Adverse events			KI, PL	KI, PL	KI, PL	KI, PL	KI, PL	
GQ 4: Issues and Future Directions								
a. Future diffusion of the modality?				KI			KI	KI
b. Economic and ethical considerations?	KI			KI				KI
c. Final decisions about ordering?	KI			KI				
d. Areas of uncertainty/priority research questions?				KI	KI		KI	KI

CT = computed tomography; F-FMISO = F-fluoromisonidazole; FDA = U.S. Food and Drug Administration; FDG = fluorodeoxyglucose; FES = fluoroestradiol; FLT = fluorothymidine; GL = gray literature; GQ = guiding question; KI = Key Informant; MRI = magnetic resonance imaging; PET = positron emission tomography; PL = published literature

Table 3. Overview of published literature (n=16[a])

	Bone Scan (n=2)	MRI (n=4)	CT (n=6)	FDG-PET or FDG-PET/CT (n=10)	FLT-PET/CT (n=4)	F-FMISO PET/CT (n=1)	FES-PET/CT (n=2)	Total (n=16)
Study Population								
United States	**1**	**2**	**1**	**4**	**1**	**0**	**2**	**7**
Europe	**1**	**2**	**5**	**5**	**3**	**0**	**0**	**8**
Asia	**0**	**0**	**0**	**1**	**0**	**1**	**0**	**1**
Study Type								
Cohort (retrospective)	2	1	2	6	0	0	2	7
Cohort (prospective)	0	3	4	4	4	1	0	9
Randomized control trial	0	0	0	0	0	0	0	0
Comparators[b]								
Tracer uptake vs. anatomic imaging	2	3	6	4	3	0	1	7
2 tracer uptakes	0	0	0	1	0	1	0	1
Tracer uptake vs. biomarkers	0	0	0	2	2	0	0	4
Outcomes[c]								
Tumor response	2	4	6	9	4	1	2	15
Progression-free survival	0	0	0	3	0	0	0	3
Overall survival	1	3	3	5	0	0	0	6

CT = computed tomography; F-FMISO = F-fluoromisonidazole; FDG = fluorodeoxyglucose; FES = fluoroestradiol; FLT = fluorothymidine; MRI = magnetic resonance imaging; PET = positron emission tomography

[a] Seven studies included greater than one type of imaging

[b] Five studies did not include comparators of imaging

[c] Some studies reported greater than one outcome

Table 4. Abstracted data from published literature

Author Year	Study Design	Inclusion/ Exclusion Criteria	N	Age (mean, range)	Imaging Modalities	Comparators	Tumor Response	Overall Survival	Timing Outcome Measures	Setting	Location
Buijs 2007[9]	Retrospective case series	MBC; receipt of MRI	14	57 (41-81)	MRI	None	NA	25 months	3 years	Single institution	United States
Cachin 2006[10]	Retrospective cohort	MBC; post-stem cell transplant PET scans	47	44 (26-60)	FDG-PET; CT, ultrasound, mammogram, bone scan	FDG-PET vs. conventional imaging)	Conventional imaging: 37% complete response; FDG-PET, 72% achieved complete response.	19 months	87 month	Single institution	France
Cheng 2013[11]	Prospective cohort	Post-menopausal, ER+ BC, stages II-IV	12	65.1 (55-82)	FDG-PET/CT; F-FMISO-PET/CT	FDG-PET/CT vs. F-FMISO-PET/CT	FDG did not correlate with clinical outcomes; F-FMISO did correlate (r=0.77)	NR	3 month	Single institution	China
Contractor 2012[12]	Prospective cohort	MBC	5	NR	FLT-PET/CT	Change in FLT uptake vs. change in CTCs	FLT uptake correlated with decrease CTCs	NR	2 weeks	Single institution	United Kingdom
Contractor 2011[13]	Prospective cohort	Stage II-IV BC with lesion outside bone/liver	20 (9 with stage IV)	54 (41-69)	FLT-PET/CT	FLT-PET SUV vs. anatomic response from CT	Reduction SUV associated with lesion size changes	NR	3 cycles of treatment	Single institution	United Kingdom
De Giorgi 2009[14]	Retrospective cohort	MBC	102	55.5 (SD 10.8)	FDG-PET/CT	FDG SUV vs. CTCs	CTC levels correlated with FDG uptake	15.7 +/- 7.8 months	9-12 weeks	Single institution	United States
Dose Schwartz 2005[15]	Prospective cohort	MBC	11	49 (34-68)	FDG-PET	FDG-PET vs. conventional imaging	FDG uptake correlated with conventional imaging response	14.5 months	27 weeks	Single institution	Germany
Haug 2012[16]	Prospective cohort	MBC to liver and life expectancy of >3 months	58	58 (SD 11)	FDG-PET/CT; CT, MRI of liver	FDG-PET vs. CT and MRI	NR	47 weeks	27 weeks	Single institution	Germany

Author Year	Study Design	Inclusion/ Exclusion Criteria	N	Age (mean, range)	Imaging Modalities	Comparators	Tumor Response	Overall Survival	Timing Outcome Measures	Setting	Location
Huyge 2010[17]	Retrospective cohort	MBC to bone with 2 PET/CTs	25	52 (37-72)	FDG PET/CT	FDG-PET/CT vs. CA15-3 or CEA	28% concordance PET/CT and tumor markers	NR	3 months	Single institution	Belgium
Kenny 2007[18]	Prospective cohort	Stage II-IV BC; life expectancy >3 months	5 stage IV	54 (36-80)	FLT-PET/CT	FLT-PET/CT 1 week after therapy initiation to clinical response (as measured by PET) at 60 days	FLT response correlated with clinical response. FLT response preceded tumor size change	NR	60 days	Single institution	United Kingdom
Linden 2006[20]	Retrospective cohort	MBC, ER + cancer with > 6 months followup	47	56 (35-76)	FES-PET	FES-PET vs. clinical response	Correlation between FES SUV and clinical response	0 patients had complete response to endocrine therapy; 23% had partial response	6 months	Single institution	United States
Linden 2011[19]	Retrospective cohort	MBC to bone, salvage endocrine therapy	27	55 (28-77)	FES-PET	None	NR	NR	6 weeks	Single institution	United States
Mortazavi-Jehanno 2012[21]	Prospective cohort	MBC with endocrine therapy	22	58 (40-82)	FDG PET/CT	Progression free, overall survival by different levels of SUV max	NR	55 months partial response; 71 months stable disease; 52 months progressive disease group (NSD)	4 years	Single institution	France
Pio 2006[22]	Prospective cohort	MBC	14	NR	FLT-PET	Compared FLT uptake to CA27.29 tumor marker levels and tumor size by CT	FLT uptake good predictor of change in tumor size on CT; also correlated with change in CA27.29	NR	5.8 months	Single institution	United States

Author Year	Study Design	Inclusion/ Exclusion Criteria	N	Age (mean, range)	Imaging Modalities	Comparators	Tumor Response	Overall Survival	Timing Outcome Measures	Setting	Location
Specht 2007[23]	Retrospective cohort	MBC to bone with 2 PETs	28	51 (30-68)	FDG-PET	Time to progression by level of SUV max	Changes in FDG SUV associated with time to progression	NR	17.5 months; only 1 death	Single institution	United States
Tateishi 2008[24]	Retrospective Cohort	MBC to bone with PET/CT	102	55 (25-89)	FDG-PET/CT	Baseline vs. post-treatment tumor factors	SUV decrease predicted response duration	NR	15 months	Single institution	United States

BC = breast cancer; CA15-3 = cancer antigen 15-3; CA27-29 – cancer antigen 27-29; CEA = carcinoembryonic antigen; CT = computed tomography; CTCs = circulating tumor cells; ER+ = estrogen receptor positive; F-FMISO = F-fluoromisonidazole; FDG = fluorodeoxyglucose; FES = fluoroestradiol; FLT = fluorothymidine; MBC = metastatic breast cancer; MRI = magnetic resonance imaging; NA = not applicable; NR = not reported; NSD = no significant difference; PET = positron emission tomography; SD = standard deviation; SUV = standardized uptake value

Table 5. Overview of gray literature findings

Website	Identifier	Type(s) of Imaging	Institution	Area(s) of imaging	Study Status Nov 2013
Clinicaltrials.gov	NCT01621906	MRI, FLT-PET	Memorial Sloan-Kettering Cancer Center, New York, United States	Brain Metastases	Recruiting
Clinicaltrials.gov	NCT01805908	111 Indium-Pertuzumab SPECT-CT	Ontario Clinical Oncology Group, Canada	Whole body	Not yet recruiting
Clinicaltrials.gov	NCT01627704	FES-PET	Assistance Publique-Hopitaux de Paris, France	Whole body	Recruiting
NIH Reporter	5P01CA042045-24	FLT-PET; MRI; FES-PET	University of Washington, Seattle, WA, United States	Whole body	Ongoing

CT = computed tomography; FES = fluoroestradiol; FLT = fluorothymidine; MRI = magnetic resonance imaging; PET = positron emission tomography; SPECT = single-photon emission computed tomography

Summary and Implications

Currently, all published reports pertaining to imaging evaluation of treatment response among metastatic breast cancer patients are limited to small, single-institution, nonrandomized studies. These reports, along with Key Informant opinions, indicate that FDG-PET/CT is the imaging modality of choice for assessing tumor response among metastatic breast cancer patients over conventional anatomic imaging (which includes CT, MRI, and bone scintigraphy). This preference is due to the fact that FDG-PET/CT can provide critical, immediate information regarding functional tumor response to chemotherapy or hormone therapy by measuring changes in tumor metabolism, whereas conventional anatomic imaging can only demonstrate gross morphologic changes of tumors in a delayed fashion. Moreover, early evidence suggests that the metabolic response assessed by FDG-PET/CT after initial cycles of chemotherapy may be predictive of progression-free survival as well as overall survival among metastatic breast cancer patients.

Nevertheless, conventional anatomic imaging by CT, MRI, and bone scintigraphy were the most common comparators in studies evaluating the ability of FDG-PET/CT to determine tumor response and are also considered appropriate care. The choice of imaging modality for conventional anatomic imaging is dependent upon the location of known metastases (e.g., MRI is best for evaluating brain metastases, CT is best for evaluating lung metastases, and bone scintigraphy is best for evaluating skeletal metastases). The few studies evaluating specific sites of breast cancer metastases pertained to the bone, demonstrating improved response detection for PET/CT over conventional imaging. However, larger-scale studies are required to truly demonstrate the comparative effectiveness of PET/CT and conventional anatomic imaging for specific sites of breast cancer metastases with regard to outcomes such as progression-free survival, changes in treatment, and decreased chemotoxicity, with earlier stoppage of ineffective therapies.

The major limitation noted by both the available studies and Key Informants regarding PET/CT for evaluating treatment response is the mechanism of FDG, the only FDA-approved radiotracer. FDG is an indicator of glucose metabolism within cells rather than a direct measure of tumor proliferation. Small pilot studies have reported on the efficacy of several novel tracers that may be able to measure tumor behavior at the molecular level more directly. With a majority of breast cancer patients having estrogen-receptor positive disease, FES may have greater ability than FDG to predict the response of metastatic breast cancers to hormonal therapy (e.g., tamoxifen) and to help guide treatment decisions. FLT is another novel radiotracer that was developed as a marker for cellular proliferation. It is not as susceptible to early inflammatory response to therapy as FDG and may be better at measuring early treatment response. Future research on such novel radiotracers may help clarify heterogeneous breast cancer tumor biology and allow discovery of treatments that might be more successful in improving outcomes.

Beyond using conventional anatomic imaging as a comparator to PET/CT, a few pilot studies have also attempted to evaluate the efficacy of measuring CTCs as biomarkers for therapeutic monitoring in metastatic breast cancer patients. Early data is inconclusive as to whether measuring CTCs has added value beyond functional PET/CT imaging for assessing immediate response to chemotherapy. With regard to new imaging modalities, PET/MRI may hold promise in the evaluation of metastases to the brain; however, it is not currently in wide use. Both biomarkers like CTCs and novel imaging modalities like PET/MRI warrant further development and evaluation in select subpopulations of metastatic breast cancer patients.

The most glaring knowledge gap with regard to imaging evaluation for treatment response in metastatic breast cancer is the evaluation of patient-centered outcomes. None of the published studies examined how the imaging experience or imaging findings affected patient satisfaction, patient anxiety levels, or other outcome measures that may be of central importance to metastatic breast cancer patients beyond survival benefit. Based on Key Informant input, metastatic breast cancer patients are currently under-informed regarding the role of medical imaging in determining treatment response and its ability to guide treatment decisions. Patients are also uninformed with regard to the alternatives to monitoring response by imaging. Future research efforts should address patient-centered outcomes measures associated with imaging evaluation for treatment response.

Finally, no studies addressed the issue of costs associated with imaging evaluation for treatment response for metastatic breast cancer. However, if PET/CT can correctly predict response as early as the first cycle of chemotherapy, then the relatively high cost associated with the advanced imaging exam may be outweighed by the potential cost savings from avoiding multiple additional cycles of ineffective chemotherapy and associated potential chemotoxicity. Out-of-pocket costs associated with imaging evaluation were also a concern among patients according to our Key Informants. The associated direct and indirect costs of PET/CT compared with conventional imaging should be examined in parallel with outcomes of future studies in order to determine the true value of different imaging modalities for evaluating treatment response among metastatic breast cancer patients.

Next Steps

Key Informants identified future research needs in several areas that they thought would have large impacts on clinical decisionmaking regarding imaging for treatment evaluation of metastatic breast cancer.

Intermediate and Long-Term Outcomes

Several Key Informants were interested in research that examines clinical and patient-centered outcomes to determine the impact that choice of imaging technologies has on survival, treatment selection, cost, and quality of life. Key Informants were also interested in examining how often more advanced imaging (e.g., PET/CT scans) should be conducted to evaluate treatment in order to lead to the best intermediate and long-term outcomes. Because metastatic breast cancer cannot be cured, the ultimate goal of treatment is to prolong survival with the least reduction in quality of life. Ideally, research into intermediate and long-term outcomes would identify imaging that indicates when treatments are not working as soon as possible so treatment can be stopped and potentially toxic side effects can be minimized and other forms of treatment can be pursued. To research this, women with metastatic breast cancer could be randomized to different imaging modalities prior to beginning treatment and they would continue to receive the same type of imaging at varying intervals to attempt to assess how the timing of imaging affects outcomes. Women would be followed until death or 3 years after diagnosis and cancer recurrences and treatment selections could be assessed from electronic medical records. Additionally, all costs incurred during the follow-up period could be compared between the different imaging modalities. Women could also be surveyed at six-month intervals to assess quality of life. The time and cost that would be necessary to conduct such a study would be substantial and confounding factors, such as patient and physician imaging and treatment preferences, might make a traditional, multi-institution randomized trial methodologically difficult.

Alternative approaches to examining intermediate and long-term patient-centered outcomes include the use of more adaptive trial designs, such as a pragmatic trial design that allows greater freedom regarding patient and physician imaging and treatment decisions. Even a prospective observational study design involving multiple institutions would provide valuable information regarding the effects of imaging modalities and the frequency of imaging on outcomes. A quality-of-life survey instrument can be easily implemented in either the pragmatic trial or prospective observational study designs to capture patient perspectives on treatment evaluation by imaging. Finally, decision analysis and simulation modeling may have a critical role in estimating the effects of imaging modality and frequency on the intermediate and long-term outcomes for metastatic patients given the time and cost barriers for performing traditional randomized trials.

Improving Communication with Patients

Additionally, studies that focused on improving communication to patients regarding imaging for the purpose of assessing treatment for metastatic breast cancer would be of interest. One option to begin to explore this topic would be to convene focus groups of women who are currently undergoing or have recently completed treatment for metastatic breast cancer and ask targeted questions about their experiences of patient-physician communication about imaging. These groups could help researchers gain understanding about the particular research questions that are important to this patient population and would identify the key patient-centered outcomes that should be studied through the aforementioned potential study designs.

Personalized Medicine

Key Informants were also interested in imaging that could characterize tumors at the genetic or proteomic level and allow treatments to be specific to particular types of breast cancer. Truly personalized imaging for treatment response would require further development of new radiotracers specific to the biological nature of individual breast cancers. More rigorous evaluation of novel radiotracers such as FES and FLT are needed to determine their comparative effectiveness to standard FDG use with PET/CT in specific patient subpopulations.

Blood Tests to Evaluate Treatment

Several Key Informants indicated that research on biomarkers that could evaluate treatment response and obviate the need for imaging would be greatly useful. There is currently insufficient evidence regarding CTCs and whether their measurement can help predict survival time for metastatic breast cancer patients. There is also insufficient evidence regarding whether measuring such blood tumor markers can guide treatment choices for metastatic breast cancer better than current use of advanced imaging modalities. Future research efforts should focus on the comparative predictive power of CTCs for treatment response and survival versus PET/CT and/or anatomic imaging for treatment response.

Acronyms and Abbreviations

BD	breast cancer
CA15-3	cancer antigen 15-3
CA27-29	cancer antigen 27-29
CEA	carcinoembryonic antigen
CT	computed tomography
CTC	circulating tumor cell
ER+	estrogen receptor positive
FDA	U.S. Food and Drug Administration
FDG	fluorodeoxyglucose
FDG-PET	fluorodeoxyglucose positron emission tomography
FES	fluoroestradiol
F-FMISO	F-fluoromisonidazole
FLT	fluorothymidine
GL	gray literature
KI	Key Informant
MBC	metastatic breast cancer
MRI	magnetic resonance imaging
NA	not applicable
NR	not reported
NSD	no significant difference
PET	positron emission tomography
PET/CT	positron emission tomography/ computed tomography
PET/MRI	positron emission tomography/magnetic resonance imaging
PL	published literature
SD	standard deviation
SPECT	single-photon emission computed tomography
SUV	standardized uptake value

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